THE STUDY OF A NEW ANTIBIOTIC, AZTREONAM, IN THE TREATMENT OF PULMONARY EXACERBATIONS IN CYSTIC FIBROSIS PATIENTS

by

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FINAL READING APPROVAL

TO THE DOCTOR OF PHARMACY COMMITTEE OF THE UNIVERSITY OF UTAH COLLEGE OF PHARMACY:

I have read the clinical research project report of John Merlin Benson in its final form and have found that 1) its format, citations, and bibliographic style are consistent and acceptable; 2) its illustrative materials including figures, tables, and charts are in place; and 3) the final manuscript is satisfactory to the Supervisory Committee and is ready for submission to the Doctor of Pharmacy Committee.

June 24, 1986
Date

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UNIVERSITY OF UTAH COLLEGE OF PHARMACY

SUPERVISORY COMMITTEE APPROVAL

of a clinical research project report submitted by

John Merlin Benson

We, the undersigned, have read this clinical research project report and have found it to be of satisfactory quality for a Doctor of Pharmacy Degree.

June 24, 1986
Date

Chairman, Supervisory Committee

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I dedicate this manuscript to my wife, Holly. Without her love and patience, the last four years would have been impossible. I am also grateful to my mother for her constant belief in me.

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Introduction

Cystic fibrosis is a genetically inherited disease that occurs in one out of every 2000 live, caucasian births, and is the most common lethal, genetic disease of caucasians.[1] The inheritance of this disease appears to follow an autosomal recessive pattern, and approximately five percent of Americans are asymptomatic carriers of the cystic fibrosis gene. The majority of cystic fibrosis patients present with a triad of characteristic signs: obstructive pulmonary disease, pancreatic achylia, and increased sweat sodium chloride concentration. Pulmonary complications have accounted for as much as 90% of the mortality associated with cystic fibrosis,[1] and recurrent pulmonary infections requiring hospitalization continue to be the major cause of the morbidity, mortality, and expense that these patients and their families suffer.

Pulmonary infections in cystic fibrosis patients are often caused by *Staphylococcus aureus* early in the disease, but as the disease progresses over time, most patients eventually become infected and/or colonized with *Pseudomonas aeruginosa*,[1] a gram-negative microorganism with a known propensity for antimicrobial resistance. *Pseudomonas aeruginosa* is also a major pathogen in other patient populations such as patients with malignancy, burn and trauma patients, and otherwise immunocompromised hosts, but cystic fibrosis patients have a much higher prevalence of *Pseudomonas aeruginosa* infection, as high as 70%.[2] The pathogenicity of this organism has been recognized for many years,[3] and resistance to antibiotics via ß-lactamase production and other mechanisms has long been a problem. The virulence of *Pseudomonas aeruginosa* has been attributed to both direct tissue damage by bacterially produced toxins and enzymes (e.g., exotoxin A, cytotoxin, exoenzyme S, protease, elastase, and phospholipase C), and to activation of specific (antibody and complement) and nonspecific (inflammation) host immune responses.[4,5] In addition, antibody to *Pseudomonas aeruginosa* exotoxin A has been demonstrated in the serum of patients with cystic fibrosis,[4] further evidence of the role of this organism in the pathogenesis of this disease.

An unusual aspect of pulmonary infections in cystic fibrosis patients is the high rate of mucoid strains of *Pseudomonas aeruginosa* isolated from the sputum, a finding not commonly encountered in other patient populations. There are several characteristics of these strains that may contribute to the unusually high rate of relapse seen following intensive antibiotic therapy. These mucoid strains produce slime that encloses large masses of bacteria which may add to airway dysfunction and atelectasis, and may result in resistance to phagocytosis and decreased penetration of antibodies and antibiotics.[4] These mucoid strains also have been reported to have an increased intrinsic resistance to antibiotics *in vitro*,[4] although Parry and collegues[6] published conflicting data.

Current approaches to treatment of *Pseudomonas aeruginosa* pneumonia in cystic fibrosis patients usually include intensive pulmonary toilet, nutritional support, and drug therapy using a combination of ß-lactam and aminoglycoside antibiotics. Although this approach has been adopted by the majority of cystic fibrosis treatment centers, it remains controversial in light of reports which have shown conflicting results from therapy using agents with activity against *Pseudomonas* species versus treatment regimens without antipseudomonal agents.[7,8,9,10] However, in spite of data that challenge the need for antipseudomonal therapy, most clinicians continue to treat pulmonary exacerbations in cystic fibrosis patients with aggressive antimicrobial chemotherapy. In addition to the continuing problem of resistance of *Pseudomonas aeruginosa* to antibiotics, the toxicity of the aminoglycosides to the renal, cochlear, and vestibular systems is also a major concern. Clearly, the need for safer and more effective antipseudomonal agents exists. Currently, the agents with the greatest activity against *Pseudomonas aeruginosa* are piperacillin, azlocillin, ceftazidime, cefsulodin, cefoperazone, amikacin, tobramycin, imipenem, and aztreonam.[5]

Aztreonam is the first of a new class of ß-lactam antibiotics called the monobactams. The monobactam antibiotics differ from other ß-lactam antibiotics in that they are completely synthetic in origin, and the ß-lactam ring is not fused to another ring system as in the penicillins

and cephalosporins (see Figure). Hence, these molecules are monocyclic ß-lactams, from which the name monobactam was derived. Aztreonam also differs from other ß-lactam antibiotics in its spectrum of activity by being active almost exclusively against gram-negative aerobic bacteria. The mechanism of action of aztreonam is very similar to the other ß-lactam antibiotics; it binds to penicillin binding proteins (PBP's) to inhibit bacterial cell wall synthesis. Aztreonam binds to PBP 3, inhibiting the ability of bacterial cell wall to septate during cell division, resulting in long filamentous cells and eventually cell death. The spectrum of activity of aztreonam includes most *Enterobacteriaceae*, *Neisseria* species, and *Haemophilus* species, and it has significant activity (minimum inhibitory concentration of 90% of organisms [MIC_{90}] < 16 mcg/ml) against *Pseudomonas aeruginosa*, *Enterobacter* species, and *Serratia marcescens*.[11]

Aztreonam has been investigated in the treatment of a variety of infections, including infections of the urinary tract, bacteremia, skin and deep soft tissue, chronic osteomyelitis, septic arthritis, abscesses, pneumonia, postpartum endometritis, and intraabdominal infections.[11,12,13] Aztreonam has been effective in the treatment of gram-negative infections as single-agent therapy.[11] In phase I, II and early phase III trials, aztreonam has shown little or no potential for renal toxicity and appears to cause less diarrhea than conventional therapy due to less alteration of normal gut flora.[13] Adverse reactions, like other ß-lactam antibiotics, have been minimal in clinical trials to date. In multiple-dose studies, aztreonam has shown a number of effects, including local reactions such as phlebitis or swelling in 2.4 percent of patients treated, rash and/or pruritis in 1.6 percent, nausea and/or vomiting in 0.9 percent, and diarrhea in 0.8 percent of patients.[12] Transient elevations in liver enzymes also have been reported, although inconsistently.[11,12] Enterococcal superinfection has been reported following treatment with aztreonam.[14] Following intravenous administration, aztreonam exhibits first-order elimination kinetics with an elimination half-life of approximately 1.7 hours. The drug is 56 percent bound to serum proteins, and 60 to 70 percent of a dose is renally excreted.[15]

Purpose. The purpose of this study was to examine the efficacy of aztreonam in the treatment of gram-negative pneumonia in patients with cystic fibrosis. Aztreonam has been shown in preliminary studies to be effective in the treatment of *Pseudomonas aeruginosa* infections. A more effective antipseudomonal agent may help increase the life expectancy of cystic fibrosis patients, as well as help control the high health care costs these patients incur.

Materials and Methods

This study design was open-label with no controls. The study received institutional Review Board approval prior to enrolling any patients. Participants in this study were consecutively selected from cystic fibrosis patients admitted to the pediatrics unit at University Hospital, Salt Lake City, Utah, for parenteral antibiotic treatment of pulmonary exacerbation of cystic fibrosis. Informed written consent (Appendix B) was obtained for all patients prior to beginning the study either from the patients (18 years of age or older), or their legal guardians. For those cases in which the patient was considered a competent minor (12 years of age or older), written assent from the patient was also obtained. Inclusion criteria were as follows:

1. Six years of age or older
2. Documented gram-negative pulmonary infection by sputum culture
3. Documented sensitivity of the infecting organism to aztreonam
4. No history of anaphylactic (type 1) reaction to penicillins
5. Non-lactating or non-pregnant females
6. No evidence of severe hepatic dysfunction as judged by:
   - -aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than three times the upper limit of normal
   - -total serum bilirubin greater than 1.5 times the upper limit of normal
7. No concurrent severe disease, such as neoplasm, that may limit survival during the study period
8. No granulocytopenia (absolute neutrophil count less than 1000) or other significant immunodeficiency
9. Serum creatinine level less than the upper limit of normal for age and weight per University Hospital standard, and no other evidence of renal dysfunction
10. No evidence of heart failure
11. No other condition making the patient unsuitable for enrollment in the study

Initial assessment. All patients received an initial assessment on admission to the study which consisted of a complete history and physical examination, chest roentgenogram,

complete blood count with white cell differential, 20-channel blood analysis (including: sodium, potassium, chloride, bicarbonate, creatinine, blood urea nitrogen, glucose, calcium, phosphate, uric acid, AST, ALT, gamma-glutamyl transpeptidase, lactic dehydrogenase, alkaline phophatase, creatine kinase, total protein, albumin, and direct and total bilirubin), urinalysis, and sputum sample (obtained before starting antibiotic therapy) for quantitative microbiology and sensitivity testing. A complete blood count with white cell differential, 20-channel blood analysis, urinalysis, and sputum culture and sensitivity were repeated every five days during therapy and on the last day of therapy, and sputum culture and sensitivity again at the follow up assessment 7 to 14 days after cessation of therapy.

Processing of sputum samples. Sputum samples obtained before therapy was started, every five days during therapy, on the last day of therapy, and at the follow up visit were each subjected to the same process. Acceptable samples were defined as having fewer than ten epithelial cells per low power (100x) field and more than 25 white blood cells per low power field. First, sputum was diluted into three tubes containing tryptic soy broth (TSB) to concentrations of 0.01 ml sputum per 0.1 ml of TSB (1:10 dilution), 0.01 ml sputum per 1 ml of TSB (1:100 dilution), and 0.001 ml sputum per 1 ml of TSB (1:1000 dilution). Then, from the undiluted sputum and each of these dilutions, 0.01 ml and 0.001 ml volumes were plated out on blood, chocolate, and MacConkey agar plates, representing volumes of 0.01, 0.001, 0.0001, and 0.00001 ml of undiluted sputum onto these agar media. These plates were incubated for 24-48 hours at 35°C, at which time the colonies were counted. Colony counts were expressed as colony forming units (CFU) per milliliter. Individual colonies were then taken, isolated for pure culture, and identified. These isolates were placed in broth and incubated another 24 hours. The broth was then standardized to 0.5 MacFarland standard (representing 5×10^8 CFU per ml for *Pseudomonas aeruginosa*) and smeared on a Kirby-Bauer disk-diffusion plate onto which disks containing standard concentrations of the following antibiotics were placed for sensitivity testing: aztreonam, tobramycin, gentamicin, cefoperazone, moxalactam, piperacillin, and

amikacin. The isolates were also placed on serial dilution agar plates for MIC testing. Agar dilution and Kirby-Bauer plates were read after another 24 hours of incubation. Aztreonam sensitivity was defined as a disk diffusion zone size equal to or greater than 21 mm, and MIC ≤ 8 mcg/ml. Intermediate sensitivity was defined as a zone size equal to or greater than 16 mm but less than 21 mm, and MIC = 16 mcg/ml. Organisms with zone sizes less than 16 mm, and MIC ≥ 32 mcg/ml, were defined as resistant to aztreonam.

Scoring. The numerical scoring system of Beaudry, et al,[10] was used to assess the severity of the patients' pulmonary disease. This assessment was done on the first day of therapy, repeated every seven days during therapy, and again at the follow up visit. The scale consisted of zero to three points, based on severity (zero being no symptom and three being severe symptom), for each of the following areas: cough, sputum production, cyanosis, retractions on inspiration, temperature, heart rate, and respiratory rate (Appendix C). Patient progress was also assessed daily by recording vital signs (temperature, blood pressure, heart rate, and respiratory rate) every eight hours and using a second scoring system in which the patient's status was quantified using a scale from one to four, with one being no symptom and four being severe symptom, in each of the following areas: cough, rales/rhonchi, chills, consolidation/pleural effusion, decreased pulmonary function, and symptoms related to bronchitis (Appendix D).

Dosing. Following initial assessment and collection of laboratory specimens, all patients received aztreonam, 50 mg/kg IV every six hours (supplied by E.R. Squibb & Sons, Inc., Princeton, NJ). The drug was reconstituted and diluted to a concentration of less than 2 mg per 100 ml of diluent. Using a constant rate syringe pump (Harvard Mini-Infuser 100, C.R. Bard, Inc., North Reading, MA) drug was infused over approximately 30 minutes. For patients in whom gram-positive organisms were documented or strongly suspected (recent previous infection with documented gram-positive infection), an agent with the appropriate antibacterial spectrum, but without gram-negative activity, could be started in appropriate doses. All patients received chest

percussion and postural drainage five times per day, nutritional support, and oxygen and/or bronchodilator therapy when needed. Patients were not allowed to take any antibiotics during the period between the last day of therapy and the follow up visit.

Following completion of the study, all patients were assessed as to their clinical and microbiological response, according to the following definitions:

Microbiological Response

Cure: Causative organism(s) eliminated or at least one-log decrease in sputum colony count on the last day of treatment or, if no culture done at that time, within two days of the last treatment day.

Cure with relapse: Causative organism(s) eliminated or at least one-log decrease in sputum colony count at the end of treatment but recurrence of infection due to an organism of the same species during the follow up period.

Cure with reinfection: Causative organism(s) eliminated or at least one-log decrease in sputum colony count at the end of treatment but recurrence of infection due to a different organism during the follow up period.

Failure: Persistence (less than one-log decrease, no change, or increase in sputum colony counts) of causative organism(s) at end of treatment.

Superinfection: Occurrence of infection (as evidenced by clinical signs and symptoms of infection and requiring therapy) at the same site due to different pathogen(s) during aztreonam therapy.

Treatment emergent: Isolation of new nonpathogenic isolate(s) at the same site during treatment.

Subsequent infection: Emergence during treatment or at follow up of an infection at a different site.

Clinical Response

Cure: Defervescence and complete resolution of signs and symptoms of lower respiratory tract infection.

Partial response: Substantial or temporary improvement in signs and symptoms of lower respiratory tract infection without complete resolution.

Failure: Persistence or progression in signs or symptoms of infection.

Statistical analysis. Data used for statistical analyses were white blood cell counts at entry into the study, at day five of therapy, and at the end of therapy, pulmonary status scores at

entry, day seven, and follow up, daily clinical scores at entry, day five, end of therapy, and follow up, and colony counts of aztreonam-sensitive isolates of *Pseudomonas aeruginosa* at entry, day five, end of therapy, and follow up. The data were analyzed using a one-way analysis of variance with repeated measures, and followed with Scheffé's test for determination of differences between groups. Statistical significance was defined as p less than or equal to 0.05.

Results

Of 25 patients entered into the study, 23 completed at least five days of therapy according to protocol and 20 had data collected at least at entry into the study, at five and seven days of therapy, at the end of therapy, and at the follow up visit. The duration of therapy ranged from 5 to 19 days (mean = 11.5 days). Two patients were dropped from the study when they were found to be infected with gram-negative pathogenic organisms resistant to aztreonam. Data from the above 20 patients were used for analysis.

The patients ranged in age from 6 to 32 years (mean = 13.8); 14 were males and 11 were females. Demographics of all patients are presented in Table 1. With the exception of the two patients dropped from the study, all patients improved clinically during treatment with aztreonam. At least one strain of *Pseudomonas aeruginosa* was isolated from all patients, and in six patients *Pseudomonas cepacia* was found on sputum culture. Other gram-negative organisms isolated were *Escherichia coli* (two patients), *Enterobacter agglomerans* (two patients), *Enterobacter cloacae* (two patients), *Pseudomonas fluorescens* (two patients), *Haemophilus influenzae* (two patients), and *Klebsiella oxytoca* (two patients).

The mean values of the white blood cell counts, pulmonary status scores, daily clinical scores, and colony counts of *Pseudomonas aeruginosa* isolates are presented in Table 2. The white blood cell counts decreased from 10.5±3.3 (mean±S.D.) on the first day of therapy to 7.4±1.8 at the end of therapy with statistical significance ($p<0.05$), but the decreases from the first day to day five (8.6±2.6), and from day five to the end of therapy did not achieve statistical significance ($p>0.05$). Pulmonary status score decreases between the first day of therapy

(6.3±2.5) and day seven (2.5±2.1), and the first day of therapy and follow up (2.7±2.2) were both statistically significant, indicating improvement in pulmonary status. The pulmonary status scores increased slightly from day seven to follow up, but this change was not statistically significant. The daily clinical scores showed statistically significant decreases from the first day (14.6±3.0) to day five (10.1±2.4), from the first day to the end of therapy (7.7±1.7), and from the first day to follow up (9.2±3.3), also indicating improvement. Patients continued to improve after five days of therapy as shown by statistically significant improvement in clinical scores between day five and the end of therapy. Clinical scores increased between the end of therapy and follow up, and this change was also statistically significant, indicating a worsening of clinical status after therapy was stopped. Perhaps of most importance, the colony counts of susceptible isolates of *Pseudomonas aeruginosa* showed a statistically significant decrease from 4.4±3.9 $\log_{10}$ on the first day of therapy to 1.2±2.3 $\log_{10}$ at the end of therapy, but statistical significance was also achieved by the increase in colony counts from the end of therapy to follow up (4.4±3.9 $\log_{10}$), indicating persistence of the original infection or possibly reinfection. (It is coincidental that the colony counts on the first day and at follow up are identical to one decimal point.) The mean MIC of isolated mucoid strains of *Pseudomonas aeruginosa* susceptible to aztreonam was 8.5 mcg/ml, while that for the nonmucoid strains was 7.3 mcg/ml. Of the 33 isolated strains of *Pseudomonas aeruginosa* isolated on day one and/or day five of therapy and sensitive to aztreonam, 21 were eradicated by the last day of therapy, and ten of these continued to be eradicated at follow up.

Of the 20 evaluable patients, seven either had no sputum production (two) or had no growth on sputum culture (five) at the end of treatment. The two patients unable to produce sputum (patients 4 and 5) continued to be unable to produce a sputum sample at follow up, while one (patient 21) of the other five patients with sterile sputums at the end of treatment continued to have sterile sputum at follow up, and a second (patient 15) of these five patients was unable to produce sputum at follow up.

Emergence of resistance was defined as any isolate sensitive to aztreonam when first isolated which was shown to be resistant (MIC ≥ 32 mcg/ml) at subsequent culture and sensitivity testing. Of a total of 65 strains of *Pseudomonas aeruginosa* isolated during the study, three were resistant to aztreonam on initial sensitivity testing, and five were resistant at at least one subsequent sampling point after having been shown sensitive to aztreonam when first isolated. Of the six patients with resistant *Pseudomonas aeruginosa*, only one failed to improve clinically by the end of therapy. Other gram-negative organisms which were resistant to aztreonam on initial sensitivity testing were three strains of *Pseudomonas cepacia* (patients 2, 11, and 24), two strains of *Pseudomonas* species other than aeruginosa (patient 11, the species could not be identified), and two strains of *Pseudomonas fluorescens* (patients 11 and 12).

Of the 20 evaluable cases in this study, six were determined, at completion of the study, to be clinical cures and 14 partial clinical responses. Microbiological cures were achieved in eight patients, cures with relapse in eight, cures with reinfection in two, and microbiological failures occurred in two patients.

Discussion

In this study, we found aztreonam to be effective in reducing the colony counts of most gram-negative organisms, including *Pseudomonas aeruginosa*, found in sputum cultures of the patients studied. In addition, patients improved clinically as manifested by decreased clinical and pulmonary status scores, and by decreased white blood cell counts during therapy. Clinical improvement continued beyond five days of treatment as shown by statistically significant decreases in clinical scores between day five of therapy and the last day of therapy. Pulmonary status scoring was not performed at the end of therapy, but this scale may also have shown further improvement between day seven and the end of therapy, since there was little change between day seven of therapy and follow up. We did not assess the correlation between microbiological response and clinical response, but other investigators have found clinical response to be independent of microbiological response,[16] and Wientzen and collegues[7] and Nelson[17] have

observed that isolation of *Pseudomonas aeruginosa* or *Staphylococcus aureus* from the sputum of cystic fibrosis patients is as likely during asymptomatic intervals as during periods of pulmonary exacerbation.

Although improvement during therapy occurred in this study, deterioration of patient status was seen between the last day of therapy and the follow up visit at 7 to 14 days posttreatment. Colony counts of *Pseudomonas aeruginosa* isolates had increased to pretreatment levels at the follow up visit, and clinical scores were statistically significantly increased over those obtained on the last day of therapy. Our inability to permanently and consistently eradicate *Pseudomonas aeruginosa* from the sputum, in spite of *in vitro* susceptibility to the antibiotic used, is consistent with the experience of other investigators.[8,10,16,18] Inhibitors of antibiotics in sputum have been identified and may help explain why these organisms persist in spite of *in vitro* susceptibility to antibiotics, but whether these inhibitors operate at the site of infection, the bronchial wall, is unknown.[17] Although 10 of 33 strains of *Pseudomonas aeruginosa* were eradicated at follow up in our study, the time of follow up was only 7 to 14 days following cessation of treatment, whereas most other investigators have evaluated patients one to six months after drug therapy has been stopped.

The fact that our patients improved clinically despite the presence of *Pseudomonas aeruginosa* in their sputa calls into question the importance of drug therapy directed at reducing or eradicating *Pseudomonas aeruginosa* from the sputum of cystic fibrosis patients. As suggested by Wientzen and collegues,[7] the improvement in life expectancy for cystic fibrosis patients may be due as much to intensive pulmonary toilet and attention to nutritional needs as to the use of antibiotics. Also, as mentioned above, Beaudry and collegues[10] have demonstrated no difference in clinical outcome between patients treated with carbenicillin plus gentamicin and those who only received cloxacillin. Their patients improved during hospitalization regardless of the antibiotic treatment received. However, these results are not supported by the studies of Hyatt and collegues,[8] who found that patients had statistically significantly greater improvement after

treatment with oxacillin, sisomicin and carbenicillin when compared to treatment with oxacillin alone, and Wientzen and collegues[7] who found that their patients tended to do better when treated with tobramycin as opposed to placebo.

The present study does nothing to resolve the issue of whether or not to treat pulmonary exacerbation of cystic fibrosis with antipseudomonal agents since we did not include a treatment group who received no antipseudomonal agents, but it does show aztreonam to be a promising antipseudomonal agent should this eventually be shown to be the best approach. Aztreonam is at least as effective as other agents reported in the literature in reducing and eradicating *Pseudomonas aeruginosa* from the sputum of cystic fibrosis patients, and although our follow up period was only 7 to 14 days, the rate of eradication of *Pseudomonas aeruginosa* from sputum appears to exceed the rates found with most other antipseudomonal agents. However, this finding requires further verification after more *Pseudomonas* infections have been exposed to aztreonam over time.

Clinically, our patients continued to be improved at follow up compared to entry into the study as shown by statistically significant improvement of follow up clinical scores and pulmonary status scores when compared to those done on the first day of treatment, and by the lack of a statistically significant increase (worsening) in pulmonary status scores between day 7 and follow up. All 20 evaluable patients achieved at least partial clinical response during treatment with aztreonam, and all but two of these showed at least temporary microbiological cures.

One area of difficulty in this study was the microbiologic tests performed. Emergence of resistance was difficult to identify due to the uncertainty that isolates found at one sampling time were in fact the same isolates as those found at previous sampling times. This uncertainty arose from the variable morphology of *Pseudomonas aeruginosa* colonies found on the agar media and is demonstrated by the variable MIC's within a single isolate (see Appendix A). The isolates of *Pseudomonas* were also difficult to quantify, particularly the mucoid strains of *Pseudomonas aeruginosa*, and speciation was also challenging at times. For example, patient 11 had three

strains of *Pseudomonas* that could not be speciated using standard guidelines; they could only be identified as non-aeruginosa. Krilov and collegues[19] had similar difficulties in identifying *Pseudomonas* species, despite serotyping, when they studied the efficacy of imipenem in the treatment of pulmonary exacerbations of cystic fibrosis. The mucoid strains of *Pseudomonas aeruginosa* are especially difficult to count and identify due to their dominance of the agar plate. Peir[2] stated that over 80% of mucoid strains cannot even be serotyped.

Emergence of resistance was not commonly found in our study. No patient experienced clinical deterioration as a result of the emergence of a resistant strain of *Pseudomonas aeruginosa*, nor was any patient withdrawn from the study due to the isolation of a resistant strain which was initially sensitive. Emergence of resistance of *Pseudomonas aeruginosa* to aztreonam has been reported,[20,21] although the number of cases to date have been few. However, emergence of resistance is an area of major concern in antimicrobial chemotherapy, especially with *Pseudomonas aeruginosa*. While the addition of an aminoglycoside has reduced the rate of emergence of resistant strains of *Pseudomonas aeruginosa*,[16] this approach has not always been successful.[6,18,22] In fact, Sanders and Sanders,[22] and Preheim and collegues[23] have reported the emergence of strains of *Pseudomonas aeruginosa* and *Enterobacter aerogenes* that have become resistant during therapy to both aminoglycosides as well as certain ß-lactam antibiotics (moxalactam, cefotaxime, ceftazidime, and cefsulodin). This resistance pattern cannot be explained by enzyme induction as described below. Preheim and collegues[23] suggested that cross-resistance to aminoglycosides may be due to an alteration in the electron transport system resulting in diminished uptake of the aminoglycoside molecules.

A major mechanism of resistance emergence is via the induction (or derepression) of a Richmond-Sykes type 1 ß-lactamase enzyme. Emergence of resistant *Pseudomonas aeruginosa* strains by this mechanism has been reported during treatment with moxalactam, cefotaxime, aztreonam, ceftizoxime, ceftriaxone, cefsulodin, and ceftazidime,[22] agents which traditionally have had high activity against *Pseudomonas aeruginosa*. Enzyme induction

results in an overwhelming production of ß-lactamase which not only confers resistance to the original antibiotic agent, but also to the majority of other ß-lactam antibiotics, thereby rendering the organism resistant to virtually every available agent. This multiple resistance is due to a trapping effect in which the antibiotic molecules are bound by the ß-lactamase molecules and, while they are not hydrolyzed, they are prevented from binding to their sites of action, the penicillin binding proteins.[22,24] An encouraging note is that the new carbapenem, imipenem, is not affected by this type of resistance. The reason seems to be that imipenem binds to penicillin binding protein 2 (PBP2), and since there are far fewer PBP2 sites than there are PBP3, for example, much less drug is needed to bind a sufficient number of target sites to inhibit cell wall synthesis.[22] These data are tempered by the findings of Krilov and collegues[19] that showed a high rate of emergence of resistance to imipenem therapy in cystic fibrosis patients with pulmonary exacerbation. In their report, resistance was postulated to be due to (1) enzyme induction or derepression, although they did point out that imipenem has not tended to be affected by this mechanism, (2) the structure of PBP2 being altered which reduced its affinity for imipenem, or (3) the structure or function of the outer membrane porins of *Pseudomonas aeruginosa* possibly being changed which would reduce the penetration of imipenem into the cell. The sensitivity patterns of these resistant isolates to other antimicrobial agents were not reported. Such information may have helped identify whether ß-lactamase induction had occurred.

The MIC's of the mucoid strains of *Pseudomonas aeruginosa* isolated from our study patients had a geometric mean of 2.1 mcg/ml, and that of the nonmucoid strains was 3.5 mcg/ml. This difference is slight, but appears to differ with the observation made by others that mucoid strains seem to have a higher intrinsic resistance to antibiotics than nonmucoid strains.[4] Similar to our findings, Parry and collegues[6] reported that the strains of *Pseudomonas* isolated from their cystic fibrosis patients fell into one of two groups: (1) usually mucoid and highly sensitive to ticarcillin (MIC value ≤ 1.6 µg/ml), and (2) usually nonmucoid with ticarcillin MIC values of 25 to 100 µg/ml. The importance or even the existence of an intrinsic resistance to antibiotic

therapy of mucoid strains of *Pseudomonas aeruginosa* is not clarified by the results of this study. Whether mucoid strains become yet another limiting factor in the treatment of *Pseudomonas* pneumonia will require further research.

An interesting finding in this study is the fact that although several strains of *Pseudomonas* species other than aeruginosa (hereafter referred to as non-aeruginosa) were isolated from the sputum of some patients, these patients' courses seemed to be dependent on the aztreonam sensitivity pattern of the *Pseudomonas aeruginosa* isolates, regardless of the sensitivity patterns of the non-aeruginosa *Pseudomonas*. One example is patient 11 who had four strains of non-aeruginosa *Pseudomonas* in his sputum which were resistant to aztreonam, and two strains of *Pseudomonas aeruginosa* which were sensitive, and he showed partial clinical response and microbiological cure at the end of therapy. This raises the issue of whether non-aeruginosa isolates of *Pseudomonas* require specific antimicrobial therapy. In our study, *Pseudomonas cepacia* was not always regarded as a nonpathogenic organism as two patients with aztreonam-resistant *Pseudomonas cepacia* isolates in their sputum cultures were dropped from the study, although their *Pseudomonas aeruginosa* isolates were sensitive to aztreonam. However, as stated above, in spite of other resistant organisms most patients did well both clinically and microbiologically. Recent reports have suggested that *Pseudomonas cepacia* is indeed a pathogenic organism, and colonization with this organism has been associated with the rapid deterioration and death of some cystic fibrosis patients who previously had relatively mild disease.[25,26] It is interesting to note that *Pseudomonas cepacia* is rarely pathogenic in other patient populations,[26] although it is widely distributed in nature. The question of whether non-aeruginosa *Pseudomonas* infections require specific therapy cannot easily be answered. Our data suggest that *in vitro* sensitivity of *Pseudomonas cepacia* and other non-aeruginosa *Pseudomonas* isolates to the antimicrobial therapy being used may not be related to clinical improvement. However, this issue and the issue of whether or not to treat patients with antipseudomonal agents at all are only two of many problems facing the clinician who treats cystic

fibrosis patients. Whether or not there is a benefit of *Pseudomonas* -specific drug therapy independent of other therapeutic measures is the older and perhaps more pressing question. Clearly, these and other issues will require further research.

Conclusions

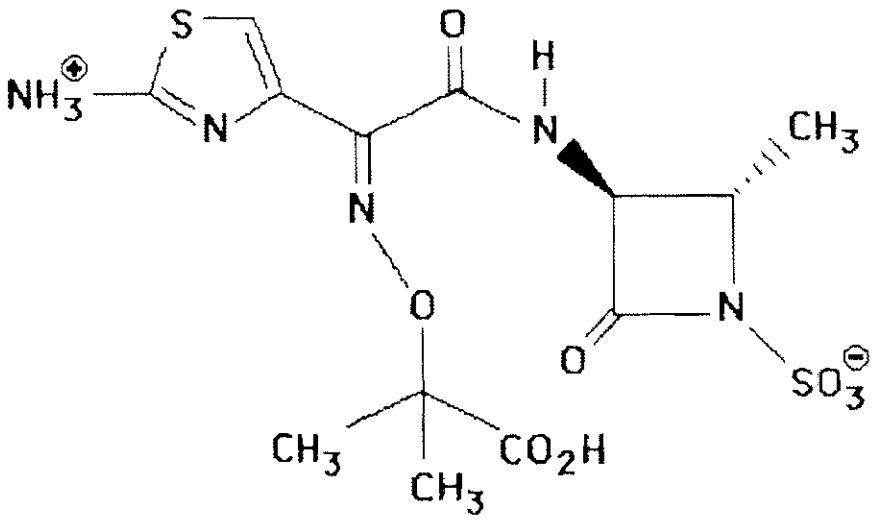
Pulmonary complications from cystic fibrosis continue to be the major cause of morbidity and mortality, as well as expense, for afflicted patients. In this study, therapy with aztreonam caused a significant decrease in bacterial cell counts, with eradication in some cases, and resulted in clinical improvement during therapy. This improvement was sustained, though only partially, for at least seven days after therapy was stopped. In this study, patients were followed only for a maximum of 14 days posttherapy. The question of whether aztreonam results in longer periods without rehospitalization than other antibiotic regimens is not answered by these data. Emergence of resistance was not commonly found in this study. Aztreonam appears to have significant promise as an antipseudomonal agent for the treatment of *Pseudomonas* pneumonia in cystic fibrosis patients, but requires further study in this population. A controlled trial comparing aztreonam to other ß-lactam antibiotics would provide additional information as to the position that aztreonam should occupy in the treatment of these infections.

The important issue of whether aztreonam would be cost effective in this setting over conventional therapy cannot be addressed at this time due to aztreonam not having received FDA approval for sale in the United States, and therefore its cost has yet to be established. FDA approval is expected shortly, however, and this is another issue that merits study.

FIGURE

FIGURE

AZTREONAM STRUCTURE



TABLES

TABLE 1. Patient demographics.

Patient	Initials	Age (yrs)	Sex	Weight (kg)	Previous pneumonias	Days of therapy
1	BA	6	M	17.0	10	8
2*	RS	15	F	50.0	4	5
3	JB	16	M	34.0	2	7
4	YB	20	F	39.4	2	9
5	KP	11	M	25.2	6	12
6	RC	14	F	39.6	1	10
7	PC	9	M	20.7	10	15
8	RP	22	M	44.5	10	15
9	RJ	6	M	16.2	2	7
10	LM	14	F	36.5	6	14
11	BF	13	M	46.8	4	14
12	KS	10	F	23.0	unknown	14
13	LG	20	F	44.4	15	9
14	FH	21	M	56.7	"many"	19
15	CS	16	M	30.0	"several"	16
16	JN	9	F	20.0	4	10
17	KM	8	F	25.0	1	14
18	SK	10	F	25.0	3	10
19	TK	12	M	40.2	1	10
20*	KP	15	M	39.2	6	5
21	AM	6	F	18.4	1	11
22	CM	10	M	28.3	0	11
23	RM	16	M	40.1	3	11
24	ND	14	F	38.6	2	14
25	EA	32	M	62.4	>40	17

*dropped due to isolation of resistant pathogenic organisms

TABLE 2. Data from 20 evaluable patients (All values are means±S.D.).

	WBC counts (x 1000)	Pulmonary scores	Clinical scores	Colony counts (log_{10} CFU/ml)
Entry	10.5±3.3	6.3±2.5	14.6±3.0	4.4±3.9
Day 5	8.6±2.6		10.1±2.4	2.7±2.4
Day 7		2.5±2.1		
End	7.4±1.8		7.7±1.7	1.2±2.3
Followup		2.7±2.2	9.2±3.3	4.4±3.9

APPENDICES

APPENDIX A

PATIENT DATA

PATIENT 1

	Entry	Day 5	End	Follow up
Pulmonary status score	12	4 (day 7)		4
Clinical score	21	15	11	9
WBC (x1000)	7.5	5.3	7.5	
Microorganisms Isolated				
Pseudomonas aeruginosa (mucoid)				
Log_{10} CFU/ml	8	4	-	9
MIC (µg/ml)	8	8	-	8
Pseudomonas aeruginosa				
Log_{10} CFU/ml	5	2	3	9
MIC (µg/ml)	8	8	8	8
Pseudomonas aeruginosa				
Log_{10} CFU/ml	4	4	4	10
MIC (µg/ml)	8	8	8	8
Pseudomonas aeruginosa				
Log_{10} CFU/ml	4	2	-	8
MIC (µg/ml)	8	8	-	8
Pseudomonas aeruginosa				
Log_{10} CFU/ml	-	2	-	-
MIC (µg/ml)	-	8	-	-

Response

Partial clinical response

Microbiological cure with reinfection

PATIENT 2

	Entry	Day 5	End	Follow up
Pulmonary status score	10	5 (day 7)		
Clinical score	20	18	18	
WBC (x1000)	5.8			
Microorganisms isolated				
Escherichia coli				
Log_{10} CFU/ml	3	-	dropped	
MIC	0.062	-	"	
Pseudomonas cepacia				
Log_{10} CFU/ml	9	9	"	
MIC	32	32	"	
Pseudomonas aeruginosa (mucoid)				
Log_{10} CFU/ml	9	9	"	
MIC	8	8	"	

Response

Partial clinical response

Microbiological failure
(Patient was dropped from the study on day 5 of therapy.)

PATIENT 3

	Entry	Day 5	End	Follow up
Pulmonary status score	6	1 (day 7)		3
Clinical score	15	9	9	11
WBC	7.1	7.4	6.2	
Microorganisms isolated				
Pseudomonas aeruginosa (mucoid)				
Log_{10} CFU/ml	8	4	3	8
MIC	0.5	64	32	16
Pseudomonas aeruginosa				
Log_{10} CFU/ml	7	4	3	8
MIC (µg/ml)	0.5	16	0.5	16
Pseudomonas aeruginosa				
Log_{10} CFU/ml	7	4	-	2
MIC (µg/ml)	0.5	16	-	8
Pseudomonas aeruginosa				
Log_{10} CFU/ml	-	4	-	3
MIC (µg/ml)	-	16	-	16
Response				
Partial clinical response				
Microbiological cure				

PATIENT 4

	Entry	Day 5	End	Follow up
Pulmonary status score	10	2 (day 7)		1
Clinical score	16	11	8	11
WBC (x1000)	16.9	7.6	7.9	
Microorganisms isolated				
Pseudomonas aeruginosa				
Log_{10} CFU/ml	4	no sputum	no sputum	no sputum
MIC (µg/ml)	16	"	"	"
Pseudomonas aeruginosa				
Log_{10} CFU/ml	4	"	"	"
MIC (µg/ml)	16	"	"	"
Pseudomonas aeruginosa				
Log_{10} CFU/ml	4	"	"	"
MIC (µg/ml)	8	"	"	"
Response				
Partial clinical response				
Microbiological cure				

PATIENT 5

	Entry	Day 5	End	Follow up
Pulmonary status score	5	2 (day 7)		0
Clinical score	15	11	7	7
WBC (x1000)	9.2	10.7	7.3	
Microorganisms isolated				
Pseudomonas aeruginosa (mucoid)				
Log_{10} CFU/ml	7	no sputum	no sputum	no sputum
MIC (µg/ml)	16	"	"	"
Pseudomonas aeruginosa				
Log_{10} CFU/ml	6	"	"	"
MIC (µg/ml)	32	"	"	"
Response				
Partial clinical response				
Microbiological cure				

PATIENT 6

	Entry	Day 5	End	Follow up
Pulmonary status score	6	0 (day 7)		3
Clinical score	15	7	7	8
WBC (x1000)	14.2	9.6	not done	
Microorganisms isolated				
Pseudomonas aeruginosa				
Log_{10} CFU/ml	9	-	not done	-
MIC (µg/ml)	0.2	-	"	-
Pseudomonas aeruginosa				
Log_{10} CFU/ml	10	-	"	-
MIC (µg/ml)	0.125	-	"	-
Enterobacter agglomerans				
Log_{10} CFU/ml	-	3	"	-
MIC (µg/ml)	-	0.125	"	-
Escherichia coli				
Log_{10} CFU/ml	-	-	"	6
MIC (µg/ml)	-	-	"	0.31

Response

Partial clinical response

Microbiological cure with reinfection

PATIENT 7

	Entry	Day 5	End	Follow up
Pulmonary status score	9	3 (day 7)		3
Clinical score	16	11	7	9
WBC (x1000)	10.9	7.9	8.6	
Microorganisms isolated				
Pseudomonas cepacia				
Log_{10} CFU/ml	8	9	9	9
MIC (µg/ml)	0.125	0.125	8	2
Pseudomonas aeruginosa				
Log_{10} CFU/ml	7	-	-	-
MIC (µg/ml)	16	-	-	-
Pseudomonas aeruginosa				
Log_{10} CFU/ml	3	-	-	-
MIC (µg/ml)	0.125	-	-	-
Pseudomonas aeruginosa				
Log_{10} CFU/ml	-	-	-	9
MIC (µg/ml)	-	-	-	0.25

Response

Partial clinical response

Microbiological cure with relapse

PATIENT 8

	Entry	Day 5	End	Follow up
Pulmonary status score	11	10 (day 7)		9
Clinical score	21	16	11	21
WBC (x1000)	13.5	14.2	6.8	
Microorganisms isolated				
Pseudomonas aeruginosa				
Log_{10} CFU/ml	9	4	5	7
MIC (µg/ml)	8	8	8	8
Pseudomonas aeruginosa (mucoid)				
Log_{10} CFU/ml	9	-	8	5
MIC (µg/ml)	32	-	64	64
Pseudomonas aeruginosa				
Log_{10} CFU/ml	-	4	-	-
MIC (µg/ml)	-	8	-	-
Pseudomonas aeruginosa				
Log_{10} CFU/ml	-	-	8	-
MIC (µg/ml)	-	-	128	-

Response

Partial clinical response

Microbiological cure with reinfection

PATIENT 9

	Entry	Day 5	End	Follow up
Pulmonary status score	4	2 (day 7)		-
Clinical score	12	8	8	-
WBC (x1000)	10.2	7.2	6.6	
Microorganisms isolated				
Pseudomonas aeruginosa				
Log_{10} CFU/ml	9	no sputum	no sputum	not done
MIC (µg/ml)	8	"	"	"
Pseudomonas aeruginosa				
Log_{10} CFU/ml	9	"	"	"
MIC (µg/ml)	8	"	"	"
Pseudomonas aeruginosa				
Log_{10} CFU/ml	9	"	"	"
MIC (µg/ml)	8	"	"	"
Pseudomonas aeruginosa				
Log_{10} CFU/ml	9	"	"	"
MIC (µg/ml)	128	"	"	"

Response

Partial clinical response

Microbiological response could not be assessed

PATIENT 10

	Entry	Day 5	End	Follow up
Pulmonary status score	6	3 (day 7)		4
Clinical score	14	9	9	9
WBC (x1000)	7.7	12.9	5.7	
Microorganisms isolated				
Pseudomonas aeruginosa (mucoid)				
Log_{10} CFU/ml	10	3	5	7
MIC (µg/ml)	8	1	16	0.5
Pseudomonas aeruginosa (mucoid)				
Log_{10} CFU/ml	10	4	6	6
MIC (µg/ml)	0.5	1	16	0.5
Pseudomonas aeruginosa (mucoid)				
Log_{10} CFU/ml	-	4	-	-
MIC (µg/ml)	-	2	-	-
Enterobacter cloaceae				
Log_{10} CFU/ml	-	-	2	3
MIC (µg/ml)	-	-	0.062	0.062
Response				
Partial clinical response				
Microbiological cure with relapse				

PATIENT 11

	Entry	Day 5	End	Follow up
Pulmonary status score	4	2 (day 7)		2
Clinical score	15	10	9	9
WBC (x1000)	11.4	6.1	5.3	
Microorganisms isolated				
Pseudomonas aeruginosa (mucoid)				
Log_{10} CFU/ml	9	7	-	8
MIC (µg/ml)	0.5	0.125	-	0.5
Pseudomonas aeruginosa (mucoid)				
Log_{10} CFU/ml	9	-	6	8
MIC (µg/ml)	0.5	-	64	0.125
Pseudomonas, non-aeruginosa (exact species could not be identified)				
Log_{10} CFU/ml	9	-	-	-
MIC (µg/ml)	2	-	-	-
Pseudomonas, non-aeruginosa (exact species could not be identified)				
Log_{10} CFU/ml	9	8	-	-
MIC (µg/ml)	128	128	-	-
Pseudomonas, non-aeruginosa (exact species could not be identified)				
Log_{10} CFU/ml	-	5	-	-
MIC (µg/ml)	-	128	-	-
Pseudomonas cepacia				
Log_{10} CFU/ml	-	-	9	8
MIC (µg/ml)	-	-	64	128
Pseudomonas fluorescens				
Log_{10} CFU/ml	-	-	7	-
MIC (µg/ml)	-	-	128	-

Response

Partial clinical response

Microbiological cure with relapse

PATIENT 12

	Entry	Day 5	End	Follow up
Pulmonary status score	5	2 (day 7)		2
Clinical score	13	9	8	8
WBC (x1000)	14.9	8.6	8.7	
Microorganisms isolated				
Pseudomonas aeruginosa (mucoid)				
Log_{10} CFU/ml	5	-	-	3
MIC (µg/ml)	0.5	-	-	4
Pseudomonas aeruginosa				
Log_{10} CFU/ml	2	-	-	3
MIC (µg/ml)	4	-	-	4
Pseudomonas aeruginosa				
Log_{10} CFU/ml	2	-	-	-
MIC (µg/ml)	8	-	-	-
Enterobacter cloaceae				
Log_{10} CFU/ml	-	2	-	-
MIC (µg/ml)	-	0.25	-	-
Pseudomonas fluoroescens				
Log_{10} CFU/ml	-	-	2	-
MIC (µg/ml)	-	-	>256	-
Response				
Partial clinical response				
Microbiological cure				

PATIENT 13

	Entry	Day 5	End	Follow up
Pulmonary status score	7	2 (day 7)		not done
Clinical score	13	10	8	"
WBC (x1000)	not done	11.5	13.4	
Microorganisms isolated				
Pseudomonas aeruginosa (mucoid)				
Log_{10} CFU/ml	8	7	8	"
MIC (µg/ml)	4	32	4	"
Pseudomonas aeruginosa				
Log_{10} CFU/ml	9	-	-	"
MIC (µg/ml)	4	-	-	"

Response

Partial clinical response

Microbiological failure

PATIENT 14

	Entry	Day 5	End	Follow up
Pulmonary status score	9	4 (day 7)		4
Clinical score	18	14	10	10
WBC (x1000)	16.8	12.4	13.5	
Microorganisms isolated				
Pseudomonas cepacia				
Log_{10} CFU/ml	5	-	-	-
MIC (µg/ml)	0.5	-	-	-
Pseudomonas cepacia				
Log_{10} CFU/ml	8	13	7	7
MIC (µg/ml)	16	16	0.125	16
Pseudomonas aeruginosa (mucoid)				
Log_{10} CFU/ml	-	2	7	8
MIC (µg/ml)	-	0.5	0.125	0.025
Pseudomonas cepacia				
Log_{10} CFU/ml	-	7	-	-
MIC (µg/ml)	-	16	-	-
Response				
Partial clinical response				
Microbiological failure				

PATIENT 15

	Entry	Day 5	End	Follow up
Pulmonary status score	6	3 (day 7)		0
Clinical score	14	10	6	7
WBC (x1000)	14	8.1	8	
Microorganisms isolated				
Pseudomonas aeruginosa				
Log_{10} CFU/ml	8	-	-	no sputum
MIC (µg/ml)	0.5	-	-	"
Pseudomonas aeruginosa				
Log_{10} CFU/ml	6	2	-	"
MIC (µg/ml)	0.5	0.5	-	"
Pseudomonas aeruginosa (mucoid)				
Log_{10} CFU/ml	6	2	-	"
MIC (µg/ml)	0.5	16	-	"
Pseudomonas aeruginosa				
Log_{10} CFU/ml	7	-	-	"
MIC (µg/ml)	0.25	-	-	"
Haemophilus influenzae				
Log_{10} CFU/ml	9	-	-	"
MIC (µg/ml)	0.125	-	-	"
Response				
Partial clinical response				
Microbiological cure				

PATIENT 16

	Entry	Day 5	End	Follow up
Pulmonary status score	6	3 (day 7)		6
Clinical score	13	8	6	12
WBC (x1000)	14.8	6.8	not done	
Microorganisms isolated				
Pseudomonas aeruginosa (mucoid)				
Log_{10} CFU/ml	3	3	-	6
MIC (µg/ml)	0.5	0.25	-	8

Response

Clinical cure

Microbiological cure with relapse

PATIENT 17

	Entry	Day 5	End	Follow up
Pulmonary status score	4	0 (day 7)		0
Clinical score	10	9	6	6
WBC (x1000)	7	6.7	7.2	
Microorganisms isolated				
Pseudomonas aeruginosa				
Log_{10} CFU/ml	10	-	-	2
MIC (µg/ml)	0.5	-	-	2
Pseudomonas aeruginosa				
Log_{10} CFU/ml	-	-	-	2
MIC (µg/ml)	-	-	-	1
Response				
Clinical cure				
Microbiological cure with relapse				

PATIENT 18

	Entry	Day 5	End	Follow up
Pulmonary status score	5	2 (day 7)		2
Clinical score	16	9	7	9
WBC (x1000)	9.8	8	7.2	
Microorganisms isolated				
Pseudomonas aeruginosa (mucoid)				
Log_{10} CFU/ml	8	5	not done	7
MIC (µg/ml)	8	8	"	4
Pseudomonas aeruginosa				
Log_{10} CFU/ml	8	-	"	7
MIC (µg/ml)	4	-	"	0.125
Pseudomonas aeruginosa (mucoid)				
Log_{10} CFU/ml	7	5	"	7
MIC (µg/ml)	4	1	"	0.25

Response

Partial clinical response

Microbiological cure with relapse

PATIENT 19

	Entry	Day 5	End	Follow up
Pulmonary status score	4	2 (day 7)		4
Clinical score	12	8	6	8
WBC (x1000)	8.2	7.4	8.4	
Microorganisms isolated				
Pseudomonas aeruginosa (mucoid)				
Log_{10} CFU/ml	9	5	not done	7
MIC (µg/ml)	0.25	0.25	"	0.25
Pseudomonas aeruginosa (mucoid)				
Log_{10} CFU/ml	9	5	"	-
MIC (µg/ml)	0.125	0.25	"	-
Klebsiella oxytoca				
Log_{10} CFU/ml	3	-	"	-
MIC (µg/ml)	0.125	-	"	-
Response				
Clinical cure				
Microbiological cure				

PATIENT 20

	Entry	Day 5	End	Follow up
Pulmonary status score	6	dropped		dropped
Clinical score	14	14	dropped	"
WBC (x1000)	18	12.3	"	
Microorganisms isolated				
Pseudomonas cepacia				
Log_{10} CFU/ml	8	6	"	"
MIC (µg/ml)	16	32	"	"
Pseudomonas cepacia				
Log_{10} CFU/ml	8	6	"	"
MIC (µg/ml)	16	6	"	"
Pseudomonas aeruginosa				
Log_{10} CFU/ml	6	-	"	"
MIC (µg/ml)	4	-	"	"
Pseudomonas cepacia				
Log_{10} CFU/ml	5	-	"	"
MIC (µg/ml)	0.125	-	"	"
Haemophilus influenzae				
Log_{10} CFU/ml	7	-	"	"
MIC (µg/ml)	0.125	-	"	"

Response

Clinical and microbiological responses were not assessed. The patient was dropped from the study on day 5.

PATIENT 21

	Entry	Day 5	End	Follow up
Pulmonary status score	5	0 (day 7)		0
Clinical score	13	8	6	6
WBC (x1000)	6.9	6.4	5.5	
Microorganisms isolated				
Pseudomonas aeruginosa				
Log_{10} CFU/ml	5	-	-	-
MIC (µg/ml)	0.25	-	-	-
Enterobacter agglomerans				
Log_{10} CFU/ml	2	-	-	-
MIC (µg/ml)	0.25	-	-	-
Response				
Clinical cure				
Microbiological cure				

PATIENT 22

	Entry	Day 5	End	Follow up
Pulmonary status score	4	3 (day 7)		2
Clinical score	12	9	6	6
WBC (x1000)	8.1	6	8.3	
Microorganisms isolated				
Pseudomonas aeruginosa				
Log_{10} CFU/ml	9	2	-	7
MIC (µg/ml)	1	0.25	-	2
Pseudomonas aeruginosa				
Log_{10} CFU/ml	-	2	-	7
MIC (µg/ml)	-	1	-	1
Response				
Clinical cure				
Microbiological cure with relapse				

PATIENT 23

	Entry	Day 5	End	Follow up
Pulmonary status score	5	2 (day 7)		2
Clinical score	11	11	8	8
WBC (x1000)	9.9	8.1	8.8	
Microorganisms isolated				
Pseudomonas aeruginosa				
Log_{10} CFU/ml	9	3	-	11
MIC (µg/ml)	4	1	-	1
Pseudomonas aeruginosa				
Log_{10} CFU/ml	8	-	-	-
MIC (µg/ml)	4	-	-	-
Pseudomonas aeruginosa (mucoid)				
Log_{10} CFU/ml	-	3	-	-
MIC (µg/ml)	-	8	-	-
Pseudomonas aeruginosa				
Log_{10} CFU/ml	-	4	-	-
MIC (µg/ml)	-	1	-	-

Response

Partial clinical response

Microbiological cure with relapse

PATIENT 24

	Entry	Day 5	End	Follow up
Pulmonary status score	8	4 (day 7)		not done
Clinical score	17	10	10	"
WBC (x1000)	6.8	9	5.3	
Microorganisms isolated				
Pseudomonas aeruginosa (mucoid)				
Log_{10} CFU/ml	7	2	-	"
MIC (µg/ml)	8	32	-	"
Pseudomonas aeruginosa				
Log_{10} CFU/ml	7	7	8	"
MIC (µg/ml)	8	8	32	"
Pseudomonas aeruginosa				
Log_{10} CFU/ml	7	-	-	"
MIC (µg/ml)	2	-	-	"
Pseudomonas cepacia				
Log_{10} CFU/ml	-	-	7	"
MIC (µg/ml)	-	-	32	"
Klebsiella oxytoca				
Log_{10} CFU/ml	6	-	-	"
MIC (µg/ml)	0.031	-	-	"
Pseudomonas aeruginosa				
Log_{10} CFU/ml	8	9	-	"
MIC (µg/ml)	16	16	-	"

Response

Partial clinical response

Microbiological failure with superinfection

PATIENT 25

	Entry	Day 5	End	Follow up
Pulmonary status score	4	2 (day 7)		3
Clinical score	11	8	6	10
WBC (x1000)	12.7	not done	6.2	
Microorganisms isolated				
Pseudomonas aeruginose (mucoid)				
Log_{10} CFU/ml	-	9	7	-
MIC (µg/ml)	-	0.5	0.5	-
Pseudomonas aeruginose (mucoid)				
Log_{10} CFU/ml	9	9	-	9
MIC (µg/ml)	0.5	0.5	-	0.5
Response				
Clinical cure				
Microbiological cure				

APPENDIX B

INFORMED CONSENT FORM

The Efficacy of Aztreonam in Cystic Fibrosis

Date: _____

PURPOSE OF THE STUDY:

The purpose of the research study in which you are being invited to participate is to evaluate the effectiveness of a new antibiotic, aztreonam, in the treatment of lung infections associated with cystic fibrosis. Aztreonam's effectiveness will be judged based on both clinical observations and laboratory tests. Ten to 15 patients will be involved in this study and all will receive aztreonam.

DESCRIPTION OF PROCEDURES:

Should you decide to participate in this study, you will receive aztreonam (instead of the usual antibiotics) for a normal course of therapy (8 to 14 days). Aztreonam will be given intravenously 4 times daily. You will receive physical examinations and blood, urine and sputum tests at the beginning of therapy, on day 7, and after completing your course of therapy. The blood tests require about one and one-half teaspoonful of blood. If the bacteria growing in your sputum are not susceptible to aztreonam, your participation in the study will end and you will be treated with other, more appropriate antibiotics.

If you are a female of child-bearing age, are sexually active and not using a reliable form of contraception you will be given a pregnancy test prior to your admission to this study. (If you are pregnant, breast feeding, or allergic to penicillin, you will not be allowed to participate in this study.)

As you will be required to return to the hospital for some post-therapy tests, we will pay you $50 for completion of this phase of the study to make up for lost work, travel time, and inconvenience.

RISKS AND BENEFITS:

The benefits of participating in this study include a more detailed and thorough evaluation of your disease and course of therapy and free treatment with a new antibiotic that may be equally or more effective than standard therapy. Risks of participating include those of venipuncture which may cause discomfort, redness, and a slight chance of infection, and those of the study drug. Aztreonam may cause rash, itching, nausea, vomiting, diarrhea and phlebitis (redness and pain at the injection site). It is also possible that aztreonam may be less effective than conventional therapy.

ALTERNATIVE CARE:

If you do not wish to participate in this study, you will receive normal care and treatment for your current infection, including the use of marketed antibiotics. Failure to participate will result in no prejudice to your current or future medical care.

CONFIDENTIALITY:

All information gathered in this study will be held in strict confidence. While such information will be used for medical and scientific purposes including publication, your identity will not be revealed. Additionally, this information will be available for inspection by the sponsor (E.R. Squibb & Sons, Inc.) and the Food and Drug Administration.

FURTHER INFORMATION:

Should you have further questions during or after the study you may contact Dr. John Bosso (581-7545 or 942-4525), Dr. Dwight Marble (581-3974), or Dr. Phil Black (581-2410). If problems arise that you do not wish to discuss with one of the investigators, you may contact the University's Institutional Review Board at 581-3655.

LIABILITY:

In the event you sustain physical injury resulting from the research project in which you are participating, the University of Utah will provide you, without charge, emergency and temporary medical treatment not otherwise covered by insurance. Furthermore, if your injuries are caused by negligent acts or omissions of University employees acting in the course and scope of their employment, the University may be liable, subject to limitations prescribed by law, for additional medical costs and other damages you sustain. If you believe that you have suffered a physical injury as a result of participating in this research program, please contact the Office of Research Administration, telephone number 581-6903.

VOLUNTARY PARTICIPATION:

Your participation in this study is totally voluntary and you are free to withdraw at any time without prejudice to further medical care.

CONSENT TO PARTICIPATE:

In signing below you agree to participate as a research subject in this stydy and acknowledge the fact that you have had a fair opportunity to ask questions about the above mentioned procedures. You will be given a copy of this form.

Patient Name: _____ Signature: _____

Parent or Guardian Signature: _____

Investigator Signature: _____

APPENDIX C

PULMONARY STATUS SCORING FORM

SYMPTOMS	POINTS	PRE TREATMENT	TREATMENT DAY 7	TREATMENT DAY 14	TREATMENT DAY 21	TREATMENT DAY 28	POST TREATMENT DAY 7-14
		MO DY YR	MO DY YR	MO DY YR	MO DY YR	MO DY YR	MO DY YR
COUGH							
None	0						
Minimal	1						
Moderate	2						
Severe	3						
SPUTUM PRODUCTION							
None	0						
Minimal	1						
Moderate	2						
Severe	3						
CYANOSIS							
None	0						
Minimal	1						
Moderate	2						
Severe	3						
RETRACTIONS							
None	0						
Minimal	1						
Moderate	2						
Severe	3						
TEMPERATURE							
⩽ 37°C	0						
37.1 - 38°C	1						
38.1 - 39°C	2						
⩾ 39.1°C	3						
HEART RATE							
⩽ 100/min	0						
101 - 120/min	1						
121 - 140/min	2						
⩾ 141/min	3						
RESPIRATORY RATE (sleeping)							
⩽ 30/min	0						
31 - 45/min	1						
46 - 60/min	2						
⩾ 61/min	3						
TOTAL POINTS							

APPENDIX D

CLINICAL STATUS SCORING FORM

KEY TO INTENSITY OF SIGNS/SYMPTOMS 1 = Normal/Absent 2 = Very Mild Changes/Slight 3 = Moderate Changes/Clearly Pathological 4 = Severe Changes/Highly Pathological				
COUGH	☐	☐	☐	☐
RALES/RHONCHI	☐	☐	☐	☐
CHILLS	☐	☐	☐	☐
CONSOLIDATION/ PLEURAL EFFUSION	☐	☐	☐	☐
DECREASED PULMONARY FUNCTION	☐	☐	☐	☐
SYMPTOMS RELATED TO BRONCHITIS	☐	☐	☐	☐
Other (specify) _____	☐	☐	☐	☐
Other (specify) _____	☐	☐	☐	☐

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CURRICULUM VITAE

June, 1986

John M. Benson

EDUCATION AND TRAINING:

Doctor of Pharmacy (expected), August 1986
University of Utah, Salt Lake City, Utah.

Including clerkships in the following areas:

- Adult Internal Medicine (2)
- Surgery
- Drug Information
- Pediatrics
- Psychiatry
- Obstetrics/Gynecology
- Rheumatology
- Family Practice Medicine

Also included: elective courses in analytical toxicology and physical assessment.

Residency in Clinical Pharmacy Practice, July 1984-June 1986
University Hospital, University of Utah, Salt Lake City, Utah.

Including clerkships in the following areas.

- Cardiology
- Clinical Management
- Infectious Diseases
- Hospital-Based Home Care
- Drug Research
- Independent Study (learning techniques to assay for drug concentrations in tissues)

Also included: being on-call for the Drug Information Center, responding to requests for pharmacokinetic monitoring, patient drug monitoring, and other drug-related questions, and working the night shift in the Intermountain Regional Poison Control Center.

Undergraduate Study in Pharmacy, September 1982-July 1984
University of Utah, Salt Lake City, Utah.
(By-passed last year of B. S. program to enter Pharm. D. program)

HONORS:

Health Sciences Center Volunteer Auxiliary Scholarship, 1984-1985.

Utah Pharmaceutical Association Award for Distinguished Service, April 28, 1984.

McKesson Leadership Award, 1983.

Roche Pharmacy Communications Award, 1986.

ACADEMIC APPOINTMENTS:

Teaching Fellow, Department of Pharmacy Practice, University of Utah, September 1985-June 1986.

Teaching Assistant, Department of Biochemical Pharmacology and Toxicology, University of Utah, September 1985-June 1986.

PROFESSIONAL EXPERIENCE:

Pharmacy Intern, Grand Central Pharmacy, Salt Lake City, Utah, September 1982-July 1983.

Pharmacy Intern, LDS Hospital, Salt Lake City, Utah, July 1983-July 1984.

LICENSURE: Pharmacy Intern, State of Utah, December 12, 1984.

RESEARCH, SCHOLARSHIP, AND OTHER CREATIVE WORKS:

Research project: The Study of a New Antibiotic, Aztreonam, in the Treatment of Pulmonary Exacerbations in Cystic Fibrosis Patients.

Developed an aminoglycoside pharmacokinetic computer program for the Apple Macintosh computer, and trained staff pharmacists in aminoglycoside pharmacokinetics as well as in the use of this program, University Hospital, University of Utah, 1985.

Editor, "Drug Information Bulletin," University Hospital, University of Utah, November 1984-January 1985.

Reviewer for Drug Intelligence and Clinical Pharmacy, March 1986.

Presentations:

"The use of dipyridamole in thallium-201 myocardial scanning," presented to the students and faculty of the Department of Pharmacy Practice, University of Utah, February 1985.

"Prostaglandin inhibition as a means of controlling preterm labor," presented to students and faculty of the Department of Pharmacy Practice, University of Utah, August 1985.

"The identification of risk factors for the development of NSAID-induced renal insufficiency," presented to the students and faculty of the Department of Pharmacy Practice, University of Utah, October 1985.

"Aminoglycoside pharmacokinetics," videotaped and presented to the pharmacy staff at University Hospital, University of Utah, November 1985.

"ß-Lactamases: New approaches to a serious problem," presented to the students and faculty of the Department of Pharmacy Practice, University of Utah, Januery 1986.

UNIVERSITY, PROFESSIONAL, AND PUBLIC SERVICE:

Professional Societies:

Student Member, Utah Pharmaceutical Association, 1982-1985.

Member, Student American Pharmaceutical Association, 1982-1985.

President, Student American Pharmaceutical Association, University of Utah Chapter, 1983-1984.

Coordinator and Program Committee Chairman, Midyear Regional Meeting, Region VIII, Student American Pharmaceutical Association, October 1984.

Student Member, Utah Society of Hospital Pharmacists, 1984-1985.

Student Member, American Society of Hospital Pharmacists, 1984-1985.

Member, American Society of Hospital Pharmacists, 1986.

College Committees:

Member, Tripartite Committee, 1983-1984.

Member, Student Advisory Committee, 1985-1986.

Hospital Committees:

Participated in the Pharmacy and Therapeutics Committee of the Medical Board, November 1985.

Participated in the Institutional Review Board, November 1985.

Public Service:

Invited to lecture to elderly groups on over-the-counter medications and their potential adverse effects by the Consumer Health Information Center, fall 1983.

Invited to lecture to a YWCA women's group on contraceptive medications by the Consumer Health Information Center, fall 1983.

Invited to lecture to classes of asthmatic children on antiasthmatic drugs by the American Lung Association of Utah, winter 1983-1984.

Invited to speak to high school seniors on pharmacy as a profession by the Speakers Bureau, University of Utah, November 1985.